
Neural Correlates of Declarative Memory for Emotionally Valenced Words in Women with Posttraumatic Stress Disorder Related to Early Childhood Sexual Abuse

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Background: Animal studies have shown that early stressors result in lasting changes in structure and function of brain areas involved in memory, including hippocampus and frontal cortex. Patients with childhood abuse-related posttraumatic stress disorder (PTSD) have alterations in both declarative and nondeclarative memory function, and imaging studies in PTSD have demonstrated changes in function during stimulation of trauma-specific memories in hippocampus, medial prefrontal cortex, and cingulate. The purpose of this study was to assess neural correlates of emotionally valenced declarative memory in women with early childhood sexual abuse and PTSD.

Methods: Women with early childhood sexual abuse-related PTSD ($n = 10$) and women without abuse or PTSD ($n = 11$) underwent positron emission tomographic (PET) measurement of cerebral blood flow during a control condition and during retrieval of neutral (e.g., "metal-iron") and emotionally valenced (e.g., "rape-mutilate") word pairs.

Results: During retrieval of emotionally valenced word pairs, PTSD patients showed greater decreases in blood flow in an extensive area, which included orbitofrontal cortex, anterior cingulate, and medial prefrontal cortex (Brodmann's areas 25, 32, 9), left hippocampus, and fusiform gyrus/inferior temporal gyrus, with increased activation in posterior cingulate, left inferior parietal cortex, left middle frontal gyrus, and visual association and motor cortex. There were no differences in patterns of

brain activation during retrieval of neutral word pairs between patients and control subjects.

Conclusions: These findings are consistent with dysfunction of specific brain areas involved in memory and emotion in PTSD. Regions implicated in this study of emotionally valenced declarative memory are similar to those from prior imaging studies in PTSD using trauma-specific stimuli for symptom provocation, adding further supportive evidence for a dysfunctional network of brain areas involved in memory, including hippocampus, medial prefrontal cortex, and cingulate, in PTSD. *Biol Psychiatry* 2003;53:879–889 © 2003 Society of Biological Psychiatry

Key Words: Positron emission tomography, memory, posttraumatic stress disorder, stress, hippocampus, frontal cortex

Introduction

Childhood sexual abuse is an important cause of posttraumatic stress disorder (PTSD) that is twice as common in women as in men (Kessler et al 1995; McCauley et al 1997). Sixteen percent of women are sexually abused in childhood (McCauley et al 1997), and PTSD related to childhood abuse and other causes affects 10% of women in this country (Kessler et al 1995). Understanding mechanisms underlying the symptoms of abuse-related PTSD may go a long way toward improving treatments for this disorder. An important aspect of the clinical presentation of PTSD patients is traumatic and negative emotionally valenced memories (Elzinga and Bremner 2002). These memories can be involuntary and are associated with considerable social and occupational dysfunction. Patients with PTSD in general show deficits in verbal declarative memory (Bremner et al 1993, 1995a), as well as a preference for remembrance of trauma-related material (McNally et al 1990).

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Several studies have assessed negatively emotionally valenced and trauma-related memory in patients with PTSD. These studies have used several different methodologies, including assessment of autobiographical memory, variants of the Stroop paradigm, distracting traumatic stimuli, and remembrance of traumatic and emotionally valenced words. Studies assessing autobiographical memory found deficits in retrieval of autobiographical memory in PTSD that were made worse after exposure to traumatic cues (combat slides and sounds) (McNally et al 1994). Several studies used variants of the Stroop task, involving naming the color of trauma-related words (e.g., “body-bag” for combat veterans or “rape” for sexual abuse survivors, where the word is in a color such as green or red). A delay in color naming for trauma words has been shown in patients with PTSD related to both Vietnam combat (McNally et al 1990, 1993, 1998; Vrana et al 1995) and rape (Cassiday et al 1992; Foa et al 1991). These findings were interpreted as being secondary to a nonconscious orientation toward trauma-related material in PTSD. One study showed that PTSD patients showed greater impairment on an attentional task when distracted by Vietnam combat pictures (but not words) (Chemtob et al 1999). Studies assessing declarative memory for emotionally valenced words have found that both positive and negatively emotionally valenced words are remembered more poorly than neutral words in normal human subjects (Moradi et al 2000). Preferential recall of trauma-related words was found in patients with both combat-related (Chemtob et al 1999) and sexual abuse-related (McNally et al 1998) PTSD relative to normal subjects. Other studies specifically looking at memory for emotionally valenced words found a preferential recall of negative emotionally valenced words in children with PTSD (Moradi et al 2000).

The pattern of general deficits in recall with a preferential recall of traumatic and emotionally valenced memory material in PTSD may be related to alterations in neural circuits in PTSD. Brain regions implicated in stress and PTSD include the hippocampus, medial and dorsolateral prefrontal cortex, and amygdala (Bremner 2002; McEwen et al 1992; Pitman 2001; Sapolsky 1996). Dysfunction of the medial prefrontal cortex (including anterior cingulate) has been hypothesized to result in a failure of inhibition of amygdala function (Morgan and LeDoux 1995; Morgan et al 1993), representing the neural correlate of a failure of extinction of fear responses that are mediated by the amygdala. Other regions, including posterior cingulate, parietal and motor cortex, and cerebellum are functionally related to these regions and may play a role in the circuitry of PTSD. Neuroimaging studies in PTSD are consistent with dysfunction in this connected network of related brain areas (Bremner et al 1998; Pitman 2001). Symptom provocation studies have found de-

creased prefrontal (Bremner et al 1997a, 1999a, 1999b; Liberzon et al 1999; Shin et al 1999), parietal, hippocampal (Bremner et al 1997a, 1999a), and temporal cortical function (Bremner et al 1997a, 1999a, 1999b), and increased function in posterior cingulate, motor cortex (Bremner et al 1999a, 1999b) and amygdala (Rauch et al 2000). Studies have also found evidence for alterations in middle/inferior frontal gyrus and cerebellum (Bremner et al 1999a, 1999b; Rauch et al 1996; Shin et al 1997, 1999). Most studies to date have relied on specific traumatic cues to activate personalized traumatic memories and PTSD symptoms in patients with PTSD.

To further assess the neural circuitry of PTSD, we have developed a task that involves retrieval of emotionally valenced word pairs. In this type of paradigm, instead of using a traditional declarative memory task, such as retrieval of word pairs like “gold-west,” which has been the standard of memory research for several decades, words with emotional valence, such as “stench-fear” are utilized (Bremner et al 2001). Assessment of the neural correlates of remembrance of emotionally valenced words is of interest from the standpoint of PTSD as a method for activating neural pathways relevant to trauma and memory. If PTSD patients demonstrate a pattern of brain activation during retrieval of emotionally valenced declarative memory that is similar to that seen during exposure to other tasks that stimulate brain networks mediating PTSD symptoms, such as exposure to personalized scripts of childhood trauma, or exposure to trauma-related pictures and sounds, then that would provide convergent evidence for dysfunction of a specific neural circuit in the processing of emotional memory in PTSD. The study of neural correlates of memory in PTSD is also relevant to the understanding of mechanisms underlying the broad range of alterations in memory function in these patients.

The purpose of the present study was therefore to use positron emission tomography (PET) in the examination of neural correlates of retrieval of emotionally valenced declarative memory in women with a history of childhood sexual abuse and the diagnosis of PTSD and women without abuse or PTSD. We selected a homogenous group of women with similar traumas and PTSD as the study population, because it is not known whether different types of trauma are associated with a different circuitry in PTSD patients. It is also not known whether there are gender differences in brain function in PTSD patients. We selected women with early abuse-related PTSD, as this is a major public health problem in the United States today. We predicted that there would be a decrement in retrieval for emotional words in human subjects in general, whereas PTSD women would show a pattern of a preferential recall of emotional words relative to control subjects. We hypothesized that retrieval of emotionally valenced words

would result in an altered pattern of brain activation in patients with PTSD similar to that seen in prior studies of exposure to cues of personalized traumatic memories. Specifically, we hypothesized that retrieval of emotionally valenced words in PTSD patients relative to non-PTSD subjects would result in decreased blood flow in medial prefrontal cortex (subcallosal gyrus and other parts of anterior cingulate), hippocampus, and fusiform gyrus/inferior temporal cortex, with increased blood flow in posterior cingulate, motor and parietal cortex, and dorso-lateral prefrontal cortex.

Methods and Materials

Twenty-one physically healthy women participated in the study. Subjects included women with a history of severe childhood sexual abuse (rape before the age of 13 years) ($n = 10$) and the diagnosis of current PTSD and women without PTSD ($n = 11$). A specific control group of women with a history of severe childhood sexual abuse but without PTSD was not included. Both PTSD patients and control subjects were recruited through newspaper advertisement. Diagnosis of PTSD was established with the Structured Clinical Interview for DSM-IV (SCID) (First et al 1995). Absence of psychiatric disorder was confirmed in the control subjects by the SCID for nonpatients. This study was approved by The Yale University Investigational Review Board and all subjects gave written informed consent for participation. All subjects were free of major medical illness on the basis of history and physical examination, laboratory testing, and electrocardiogram, were not actively abusing substances or alcohol (past 6 months), and were free of all medications for at least 4 weeks before the study. Subjects were not taken off of medication for the purposes of participating in the study. Subjects with a serious medical or neurologic illness, organic mental disorders, or comorbid psychotic disorders, retained metal, a history of head trauma, loss of consciousness, cerebral infectious disease, or dyslexia were excluded. There was no difference in age, years of education, or intelligence quotient between patients and control subjects (Table 1).

History of childhood abuse was assessed with the Early Trauma Inventory (ETI). The ETI is a 56-item, clinician-administered interview that assesses physical, emotional, and sexual abuse, as well as general traumatic events. The ETI has been demonstrated to be reliable and valid in the assessment of childhood trauma (Bremner et al 2000). Level of PTSD symptoms was measured with the Civilian Mississippi Scale, self-report measure of PTSD symptom level (Vreven et al 1995). Dissociative symptom level was assessed with the Clinician Administered Dissociative States Scale (Bremner et al 2000). Patients with PTSD had higher levels of PTSD and dissociative symptomatology, and higher levels of sexual, emotional (but not physical) abuse, and higher levels of general childhood traumas, than the control subjects. Mean scores on these measures are presented in Table 1.

Women with PTSD had a pattern of comorbidity similar to that seen in prior studies of PTSD from our group (Bremner et al 1999a, 1999b) and others. Six of ten PTSD patients (60%)

Table 1. Demographic and Behavioral Characteristics of Women with ($n = 10$) and without ($n = 11$) PTSD

	PTSD		Non-PTSD	
	Mean	SD	Mean	SD
Age (y)	40	6	38	8
Years of Education	15.1	3.6	16.6	2.9
Intelligence Quotient	110	13	115	22
Civilian Mississippi Score (PTSD)	111 ^a	19	73	7
CADSS Score (Dissociation)	16 ^a	15	0	0
ETI Score-Total	2421 ^a	1516	326	621
ETI-Sexual Abuse	192 ^a	203	32	94
ETI-Emotional Abuse	1499 ^a	899	207	408
ETI-Physical Abuse	257	431	82	176
ETI-General Trauma	472 ^a	393	4	6

PTSD, posttraumatic stress disorder; CADSS, Clinician-Administered Dissociative States Scale; ETI, Early Trauma Inventory.

^aPTSD > non-PTSD, $p < .05$.

fulfilled criteria for a past history of major depression and one of ten (10%) for current major depression based on the SCID interview. One patient (10%) fulfilled criteria for current and lifetime history of panic disorder without agoraphobia. Four patients (40%) fulfilled criteria for a past history of alcohol dependence, one (10%) for a past history of polysubstance dependence, one (10%) for a past history of marijuana and cocaine abuse. No patients had a current history of alcohol or substance abuse or dependence.

Six lists of word pairs were prepared for administration in conjunction with PET imaging. Each list contained 10 word pairs. The first two lists contained 10 neutral word pairs used for a control condition (shallow encoding) (described below); list 3 contained 10 neutral word pairs used as active condition (deep encoding) that were different than lists 1 and 2; list 4 contained the same word pairs as list 3 but in different order; list 5 contained 10 emotional word pairs that were also deeply encoded; and list 6 contained the same word pairs as list 5 but in different order. Word lists were presented in a fixed order: shallowly encoded neutral words, then deeply encoded neutral words, then deeply encoded emotional words. The reason for the fixed order was to prevent instructions related to the deeply encoded conditions from prompting subjects to remember words during the shallowly encoded conditions, and to prevent emotional states associated with the deeply encoded emotional retrieval conditions from carrying over to the neutral shallowly and deeply encoded conditions. Word pair lists for neutral and emotional deep encoding are presented in Table 2. The words consisted of nouns and verbs in common English usage. The “emotional” words were selected to be words in common usage that have fear-related or life-threatening content, with the idea that threat to life is a primary and robust emotion. In this article, the word “emotional” is used to indicate fear-related emotions, i.e., the word lists were not designed to represent other emotions, such as love or happiness. There was no difference in frequency of word usage in the English language (Zettersten 1978) and number of syllables between the words in the neutral and emotional word lists. In a separate study, we validated the fact that these words were associated with an increase in self-rated

Table 2. Neutral and Emotional Word Pairs in Declarative Memory Task

Neutral Word Pairs	Emotional Word Pairs
Metal-Iron	Blood-Hatred
Baby-Cries	Pain-Weapon
Crush-Dark	Mutilate-Beat
School-Grocery	Hurt-Bullet
Rose-Flower	Rape-Wound
Obey-Inch	Stench-Fear
Fruit-Apple	Bruise-Violate
Cabbage-Pen	Imprison-Punch
Clip-Pen	Harm-Body
Tape-Bottle	Bound-Welts

emotions, such as fear, anger, and sadness, relative to the neutral words (Bremner et al 2001).

Word pair lists were presented followed by recall during PET imaging. For the shallow neutral encoding condition, subjects were read the first two word pair lists and were asked to count the number of times they heard a word that contained the letter “D.” This was followed by PET imaging 5 minutes later during attempted retrieval. For example, if the subject was originally read the word pair “horse-apple,” they were read the word “horse” and attempted to retrieve the word “apple” at the time of the scan. Because the subjects were not instructed to remember the word pairs, they performed poorly during attempted retrieval, although they *attempted* to successfully retrieve the verbal material during the control scan. The control condition therefore controlled for attention and attempted retrieval. In the neutral deeply encoded recall condition, subjects were instructed to try and remember word pairs, and were read a separate list of 10 neutral word pairs (e.g., metal-iron) followed 5 minutes later by PET imaging during retrieval. This was repeated for the emotional recall condition using 10 word pairs with emotional content (e.g., “stench-fear”).

Each subject underwent six PET scans on a single day using methods as previously described (Bremner et al 1999a). Positron emission tomography imaging was performed on a Posicam PET camera (Positron Corp., Houston, TX) (in-plane resolution after filtering, 6 mm full width half maximum). The subject was placed in the scanner with her head held in a holder to minimize motion and positioned with the canthomeatal line parallel to an external laser light. An intravenous line was inserted for administration of [^{15}O]H $_2$ O. Following positioning within the camera gantry, a transmission scan of the head was obtained using an external $^{67}\text{Ga}/^{68}\text{Ge}$ rod source, to correct emission data for attenuation due to overlying bone and soft tissue.

Subjects then underwent scanning during retrieval of shallowly encoded and deeply encoded neutral word pairs and deeply encoded emotional word pairs. Ten sec before administration of [^{15}O]H $_2$ O, subjects received instructions regarding the retrieval of word pairs. Subjects were asked to provide the missing word of the pair with the instructions, “For instance, if I said ‘Gold-West,’ and now I said ‘Gold,’ you would say (‘West’).” Subjects then received a bolus injection of 30 mCi of [^{15}O]H $_2$ O followed 10 sec later by a PET scan acquisition which was 60 sec in length. The onset of the PET scan acquisition was timed to

correspond to the point of maximum rate of increase in uptake of tracer into the brain. Coinciding with the onset of the PET acquisition, the word pair lists were read out loud in a normal tone of voice by a research associate for a 1-min period at the rate of one word pair every 6 sec, and subjects provided the missing word of the pair. Subjects underwent two scans during retrieval of shallowly encoded neutral word pairs, two scans during retrieval of deeply encoded neutral word pairs, and two scans during retrieval of deeply encoded emotional word pairs, using word lists described above.

According to the logic of the study design, differences in brain blood flow between the deeply encoded words and the shallowly encoded words would be secondary to the specific effects of retrieval of words, while keeping other factors equal, including attention, auditory perception, comprehension of language, and attempt at retrieval. Differences between the deeply encoded emotional words and the deeply encoded neutral words would be specific to the remembrance of emotional words, controlling for retrieval as well as these other factors.

Images were realigned to the first image in the scanning session using statistical parametric mapping software (SPM96; Wellcome Neurological Institute, London, UK). The mean concentration of radioactivity in each scan was obtained as an area-weighted sum of the concentration of each slice and adjusted to the nominal value of 50 mL/min/100 g. The data were then rescaled and transformed into a common anatomic space (expressed in three dimensional x, y, and z coordinates) for statistical analysis. After transformation, images were smoothed to 16 mm full width half maximum before statistical analysis. Regional cerebral blood flow was compared in all subjects between neutral remembrance and control conditions, and between emotional remembrance and control conditions. To examine the specific neural correlates of retrieval of emotional words, blood flow between the emotional and neutral conditions was also compared. Data were analyzed using SPM96 (Friston et al 1991), with global blood flow considered as a confounding covariate, with image data sets in which the values assigned to individual voxels correspond to *t* statistic. Statistical images were displayed with values of *z* score units > 2.58 ($p < .005$) and clusters of greater than 65 contingent significant voxels. Reiman et al (1997) have found that the use of a *p* value of .005 as the limit of significance for SPM analyses is associated with the optimal reduction of Type I and Type II errors. An additional hypothesized area (hippocampus) is displayed with a $p < .01$, *z* score > 2.33 . Areas of activation were identified using standard stereotactic coordinates (Talairach and Tournoux 1988).

Results

Deeply encoded neutral words were recalled better than deeply encoded emotional (negative) words, which were in turn recalled better than shallowly encoded neutral words in the group as a whole [$F(2) = 55.08$; $p < .0001$; Duncan multiple range test: deeply encoded neutral $>$ deeply encoded emotional $>$ shallowly encoded neutral, $p < .05$]. There was no significant difference in recall performance between groups (i.e., no main effect for

diagnostic group and no group \times word type interactions). Percentage of recall (measured as the number of correctly recalled word pairs out of a possible total of 10) for PTSD patients and control subjects were as follows: neutral deeply encoded (6.4 [2.3 SD] versus 6.8 [2.2 SD]), neutral shallowly encoded (.1 [.2 SD] versus .6 [1.3 SD]), emotional deeply encoded (2.6 [2.0 SD] versus 4.0 [2.5 SD]).

Retrieval of neutral deeply encoded (neutral deep) compared with neutral shallowly encoded words in the PTSD women resulted in activation of left motor cortex ($x = -10$, $y = -24$, $z = 48$; z score = 3.02), right visual association cortex ($x = 34$, $y = -74$, $z = -10$; z score = 2.66) and right middle temporal gyrus ($x = 38$, $y = -46$, $z = -10$; z score = 2.65), with no areas of decreased blood flow. In the non-PTSD women there was activation of cerebellum ($x = 12$, $y = -88$, $z = -34$; z score = 3.82), anterior cingulate (Brodmann's area [BA] 32) ($x = 10$, $y = 32$, $z = 24$; z score = 2.47), right middle frontal gyrus (BA 46 and 10) ($x = 46$, $y = 44$, $z = 20$; z score = 2.95), and motor cortex ($x = 60$, $y = -2$, $z = 34$; z score = 2.57), with decreased blood flow in left middle ($x = -22$, $y = -18$, $z = -14$; z score = 3.10) and inferior frontal gyrus ($x = -58$, $y = 16$, $z = 0$; z score = 3.03) (BA 8, 9, and 45). When women with and without PTSD were compared directly, there were no statistically significant differences in activation during retrieval of neutral deeply encoded compared with neutral shallowly encoded word pairs at the $p < .01$ threshold of significance.

Retrieval of emotional deeply encoded words compared with neutral shallowly encoded words was associated with greater differences in activation patterns between women with and without PTSD. Women with PTSD had activation in motor cortex ($x = 66$, $y = -20$, $z = 40$; z score = 4.75), visual association cortex (BA 19) ($x = -26$, $y = -92$, $z = 28$; z score = 3.77), cerebellum ($x = 8$, $y = -62$, $z = -44$; z score = 4.22), left inferior parietal lobule (BA 40) ($x = -42$, $y = -34$, $z = 38$; z score = 3.09), right inferior (BA 45) ($x = 62$, $y = 26$, $z = 2$; z score = 3.64) and right middle (BA 21, 6) frontal gyrus ($x = 10$, $y = -2$, $z = 54$; z score = 5.12), and right inferior and middle temporal gyrus (BA 47/20) ($x = 68$, $y = -12$, $z = -24$; z score = 3.30). Women with PTSD showed decreased blood flow in an extensive area of medial prefrontal cortex involving orbitofrontal cortex (BA 11) and anterior cingulate (including subcallosal gyrus [BA 25 and BA 32]) and medial prefrontal cortex (BA 9) ($x = -10$, $y = 60$, $z = -12$; z score = 5.11). There were also decreases in left fusiform and inferior (BA 20) and middle (BA 21) temporal gyrus ($x = -52$, $y = -34$, $z = -28$; z score = 4.56) and right inferior temporal gyrus ($x = 48$, $y = -36$, $z = -20$; z score = 4.16), left middle frontal gyrus (BA 10) ($x = -40$, $y = 56$, $z = -2$; z score = 3.84)

and left hippocampus ($x = -18$, $y = -22$, $z = -18$; z score = 3.34). Women without PTSD showed activation in left inferior parietal lobule (BA 40) and sensorimotor cortex ($x = -46$, $y = -32$, $z = 36$; z score = 3.80), cerebellum ($x = 6$, $y = -88$, $z = 38$; z score = 4.76), left middle frontal gyrus (BA 10) ($x = -26$, $y = 46$, $z = 8$; z score = 3.16), and anterior cingulate (BA 32) ($x = 14$, $y = 30$, $z = 34$; z score = 3.81). Women without PTSD showed decreased blood flow in orbitofrontal cortex (BA 11) ($x = -8$, $y = 60$, $z = -16$; z score = 3.77), anterior cingulate (BA 32) ($x = -6$, $y = 42$, $z = 10$; z score = 3.80), superior and middle frontal gyrus (BA 8, 9) ($x = -10$, $y = 40$, $z = 48$; z score = 4.64; $x = 16$, $y = 66$, $z = 14$; z score = 3.52), superior and middle temporal gyrus (BA 38, 39) ($x = 28$, $y = 6$, $z = -36$; z score = 3.67), uncus ($x = 18$, $y = -4$, $z = 28$; z score = 3.58), insula ($x = 30$, $y = 22$, $z = 10$; z score = 3.61), and cerebellum ($x = -30$, $y = -82$, $z = -50$; z score = 3.20).

When women with PTSD were compared with women without PTSD during retrieval of emotional deeply encoded versus neutral shallowly encoded words, there were significant differences in brain activation in most of these regions. Specifically, women with PTSD women had greater activation in motor cortex ($x = 40$, $y = -8$, $z = 16$; z score = 3.23), visual association cortex (BA 19) ($x = -26$, $y = -94$, $z = 24$; z score = 3.84), cerebellum ($x = 28$, $y = -94$, $z = -32$; z score = 3.02), left inferior parietal lobule (BA 40) ($x = -66$, $y = -46$, $z = 32$; z score = 4.53), and right middle temporal gyrus (BA 20) ($x = 70$, $y = -32$, $z = -16$; z score = 3.83) (Figure 1). Women with PTSD showed decreased blood flow in an extensive area of medial prefrontal cortex involving orbitofrontal cortex (BA 11/47), anterior cingulate (including subcallosal gyrus [BA 25] and BA 32) and medial prefrontal cortex (area 9) ($x = 16$, $y = 22$, $z = -16$; z score = 5.61) (Figure 2). There were also decreases in left fusiform and inferior (BA 20) and middle (BA 21) temporal gyrus ($x = -50$, $y = -36$, $z = -28$; z score = 4.49) and left hippocampus ($x = -20$, $y = -4$, $z = -12$; z score = 2.33). Comparison of retrieval of emotional deeply encoded versus neutral deeply encoded words showed an essentially identical pattern of differences in activation between women with and without PTSD (Table 3).

Discussion

Performance of emotionally valenced declarative memory tasks in women with early abuse and PTSD was associated with activation of a specific network of brain regions that have been implicated in prior studies of PTSD. During retrieval of emotionally valenced words, women with childhood sexual abuse-related PTSD showed increased

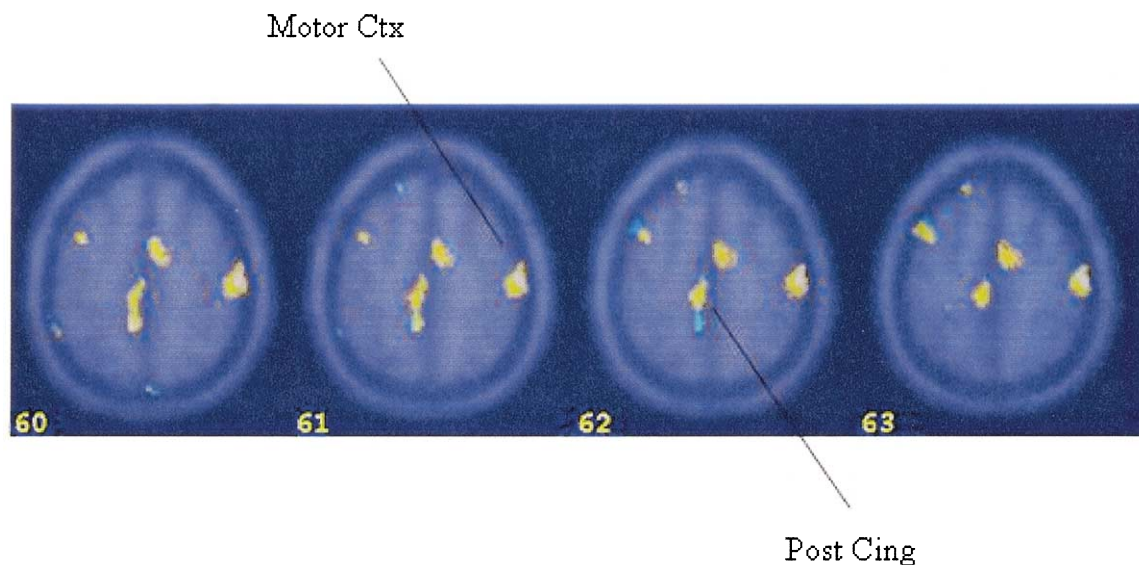


Figure 1. Statistical parametric map overlaid on a magnetic resonance imaging template of areas of significant activation (in yellow) during retrieval of emotionally valenced words in women with childhood sexual abuse and posttraumatic stress disorder (PTSD) ($n = 10$) and women without childhood sexual abuse or PTSD ($n = 11$). There were significant increases in blood flow during retrieval of emotionally valenced word pairs in PTSD relative to non-PTSD in motor cortex, visual association cortex (Brodmann's Area [BA] 19), cerebellum, left inferior parietal lobule (BA 40), and right middle temporal gyrus (BA 20). Ctx, cortex; Cing, cingulate.

activation in motor cortex, posterior cingulate, visual association cortex (BA 19), left inferior parietal lobule (BA 40), left middle/superior frontal gyrus, and right middle temporal gyrus (BA 20), with decreased blood flow in an extensive area of medial prefrontal cortex involving orbitofrontal cortex (BA 11/47), anterior cingulate (including subcallosal gyrus [BA 25] and BA 32), and medial prefrontal cortex (area 9). There were also decreases in left fusiform and inferior (BA 20) and middle (BA 21) temporal gyrus and left hippocampus in PTSD women during retrieval of emotionally valenced words, relative to non-PTSD women. These findings were seen when retrieval of deeply encoded emotionally valenced words was contrasted both with retrieval of shallowly encoded neutral words and deeply encoded neutral words.

The findings of the current study demonstrate alterations in a network of brain regions that have been implicated in previous studies of PTSD. These studies have found structural alterations in hippocampus (Bremner et al 1997b; Gurvits et al 1996; Stein et al 1997), and decreased metabolism at baseline in temporal and prefrontal cortex (Bremner et al 1997a) and parietal cortex (Semple et al 1996). Symptom provocation studies with personalized traumatic scripts, traumatic slides and sounds, masked fearful faces, and noradrenergic challenge have found decreased prefrontal (Bremner et al 1997a, 1999a, 1999b; Liberzon et al 1999; Rauch et al 1996; Shin et al 1999, 2001), parietal, hippocampal (Bremner et al 1997a, 1999a), and temporal cortical function (Bremner et

al 1997a, 1999a, 1999b), and increased function in posterior cingulate, motor cortex (Bremner et al 1999a, 1999b) and amygdala (Rauch et al 2000). Studies have also found evidence for alterations in middle/inferior frontal gyrus and cerebellum (Bremner et al 1999a, 1999b; Rauch et al 1996; Shin et al 1997, 1999). These studies have relied on specific traumatic cues to activate personalized traumatic memories and PTSD symptoms in patients with PTSD, in contrast to the current study, which assessed neural correlates of retrieval of emotionally valenced declarative memory. The findings of the current study are congruent with prior studies of PTSD in showing decreased function in medial prefrontal cortex, fusiform/inferior temporal cortex, and hippocampus, and increased function in posterior cingulate, inferior parietal cortex, and motor cortex. The current study also showed alterations in visual association cortex that were congruent with prior studies. The findings suggest that an interrelated network of brain regions, which are involved in memory function, are dysfunctional in PTSD.

Findings from the current study and other neuroimaging studies in PTSD are congruent with animal studies implicating hippocampus, medial prefrontal cortex, amygdala, and cingulate in the stress response. Stress results in structural changes in the hippocampus, a brain region involved in new learning and memory (Gould et al 1997; McEwen et al 1992; Sapolsky et al 1990), and with associated deficits in hippocampal-based declarative memory function (Arbel et al 1994; Diamond et al 1996).

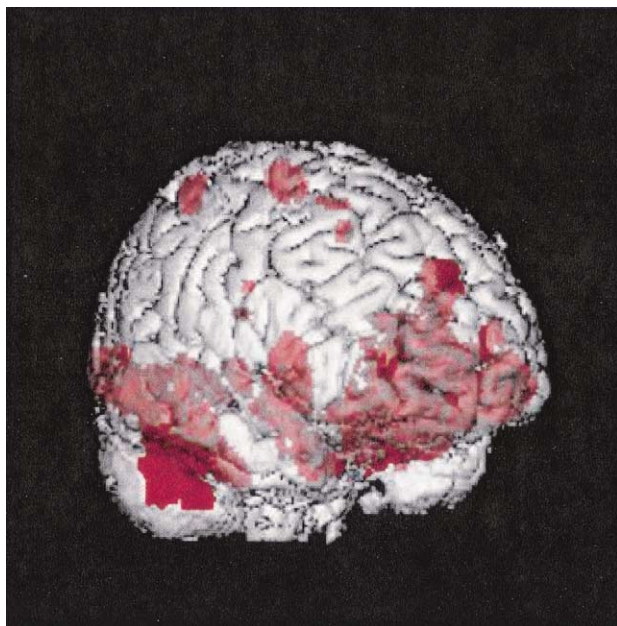


Figure 2. Statistical parametric map overlaid on a magnetic resonance imaging template of areas of significantly decreased blood flow (in red) during retrieval of emotionally valenced words in women with childhood sexual abuse and posttraumatic stress disorder (PTSD) ($n = 10$) and women without childhood sexual abuse or PTSD ($n = 11$). PTSD women showed decreased blood flow in an extensive area of medial prefrontal cortex involving orbitofrontal cortex (Brodmann's Area [BA] 11/47), anterior cingulate (including subcallosal gyrus [BA 25] and BA 32) and medial prefrontal cortex (area 9). There were also decreases in left fusiform and inferior (BA 20) and middle (BA 21) temporal gyrus and left hippocampus.

The medial prefrontal cortex has also been implicated in the stress response. Medial prefrontal cortex in the human consists of several related areas, including orbitofrontal cortex, anterior cingulate (BA 25—subcallosal gyrus, and BA 32), and anterior prefrontal cortex (BA 9). Lesions of the medial prefrontal cortex in animals resulted in a failure of inhibition of amygdala function (Morgan and LeDoux 1995; Morgan et al 1993). Given the role of the amygdala in fear responding (Davis 1992; LeDoux 1993), these findings led to the hypothesis that medial prefrontal cortex mediates extinction of fear responses. Human subjects with lesions of the prefrontal cortex showed dysfunction of normal emotions and an inability to relate in social situations that require correct interpretation of the emotional expressions of others (Damasio et al 1994). These findings suggest that dysfunction of medial prefrontal cortex may play a role in pathologic emotions that sometimes follow extreme stressors, such as childhood sexual abuse.

A region implicated in the current study that is not typically thought of as part of the fear circuit is the

cerebellum. The current study found increases and decreases in different parts of the cerebellum, depending on which condition was contrasted to retrieval of emotional words. Other functional neuroimaging studies have found either increases or decreases in cerebellar function in PTSD (Bremner et al 1999a, 1999b; Shin et al 1997), whereas one study found altered T2 relaxation time at baseline in abused children without the specific assessment of PTSD (Anderson et al 2002).

Other regions, including posterior cingulate, parietal and motor cortex, and cerebellum are functionally related to anterolateral prefrontal cortex (superior and middle frontal gyri) (Selemon and Goldman-Rakic 1988), mediating visuospatial processing that is critical to survival in life-threatening situations (Devinsky et al 1995; Vogt et al 1992). Recent PET studies have established a role for the cerebellum in attention and memory, probably mediated by its projections through the thalamus to prefrontal cortex (Ashkoomoff and Courchesne 1992; Leiner 1989). We have hypothesized that the excessive vigilance seen in PTSD is associated with increased demands on brain areas involved in visuospatial aspects of memory function and planning of response to potentially threatening stimuli (Bremner et al 1999a, 1999b).

The results of the current study suggest that declarative memory for emotionally valenced words activates a similar network of brain regions as other tasks designed to stimulate specific personalized traumatic memories (e.g., scripts or traumatic slides and sounds). This suggests that a common network of brain regions mediates declarative memory for emotionally valenced words and trauma-specific memories in patients with PTSD. In other words, emotionally valenced memory, whether declarative or autobiographical, recruits a similar network of brain areas. It is also possible that remembrance of emotionally valenced words activated personal traumatic memories or PTSD symptoms in a similar fashion to material such as personalized scripts. In the current study we did not assess PTSD symptoms or activation of personalized traumatic memories associated with remembrance of emotionally valenced word pairs. The current study also did not assess sexually abused women without PTSD, so we cannot comment on whether or not the changes are specific to PTSD, although prior studies using abused non-PTSD control subjects would suggest that this would be the case (Bremner et al 1999a; Shin et al 1999).

Patients with PTSD and control subjects did not show significant differences in retrieval performance during the PET scanning sessions. This is in contradiction to prior reports of deficits in declarative memory in PTSD (reviewed in Bremner 2002) and raises the question of whether there were clinically significant differences in memory in the patients in this study. The word pair

Table 3. Areas of Greater Increases and Decreases in Blood Flow During Retrieval of Deeply Encoded Emotional Words versus Deeply Encoded Neutral Words in Women with Abuse-Related PTSD Relative to Non-PTSD Women

z Score	p Value	Talairach Coordinates			Brain Region (Brodmann's Area)
		x	y	z	
Greater Increases in PTSD Patients Versus Normal Subjects					
4.33	<.001	64	−18	44	R precentral gyrus (4)
4.06	<.001	60	−18	52	R precentral gyrus (4)
4.08	<.001	−66	−44	34	L inf parietal lobule (40)
3.97	<.001	−26	−94	24	L cuneus/visual association cortex (19)
3.75	<.001	40	−8	16	R insula
3.65	<.001	12	−96	28	R cuneus/visual association cortex (19)
3.52	<.001	4	4	34	Posterior cingulate (24)
3.10	<.001	−8	−46	44	Posterior cingulate (31)
3.36	<.001	34	−50	−10	R lingual gyrus/parahippocampal (19)
3.34	<.001	36	−92	−26	Fusiform gyrus (18)
2.95	<.001	42	−88	−20	Fusiform gyrus (18)
3.22	<.001	−60	−64	6	L middle temporal gyrus (37)
3.18	<.001	−32	50	36	L sup frontal gyrus (9)
3.04	<.001	70	−32	−16	R middle temporal gyrus (21)
2.72	<.001	72	−34	−8	R middle temporal gyrus (21)
Greater Decreases in PTSD Patients Versus Normal Subjects					
5.71	<.001	−48	−38	−28	L fusiform/inf temporal gyrus (36)
4.00	<.001	−58	−22	−12	L fusiform/inf temporal gyrus (36)
3.07	<.001	−50	−50	−16	L fusiform/inf temporal gyrus (36)
3.11	<.001	50	−44	−26	R fusiform gyrus (36)
5.49	<.001	16	22	−14	R subcallosal gyrus (25)
4.53	<.001	26	50	−10	Anterior cingulate (32)
4.61	<.001	−30	44	−8	L middle frontal gyrus (10)
4.37	<.001	−24	50	6	L middle frontal gyrus (10)
4.05	<.001	−16	52	−4	L middle frontal gyrus (10)
3.92	<.001	−30	−88	−2	Primary visual cortex (17)
3.76	<.001	−12	−22	−8	L hippocampal region
2.98	<.01	−20	−6	−10	L hippocampal region
3.24	<.001	14	−48	68	R precuneus
3.21	<.001	4	−92	−32	Cerebellum

Regions displayed are for z score > 2.58 , $p < .005$. A single hypothesized region (hippocampus) is displayed with z score > 2.33 , $p < .01$. z scores in **bold** indicate area of greatest activation in a contiguous cluster of activated voxels that extends over several brain regions (the non-bolded z scores listed below the region with the bolded z score). R, right; L, left; inf, inferior; sup, superior; PTSD, posttraumatic stress disorder.

retrieval task used in the current study is different from prior tasks used to demonstrate memory deficits in PTSD, including paragraph recall and word-list learning. Also, the PTSD patients showed a pattern of poorer performance for deeply encoded neutral words (6% lower scores) and deeply encoded emotional words (35% lower scores) that did not achieve significance due to a small sample size.

Retrieval of emotionally valenced words was not associated with activation of all regions that have been hypothesized to participate in a network of brain regions mediating the fear response and symptoms of PTSD. Specifically, there was no evidence of involvement of amygdala or left inferior frontal gyrus. The amygdala has been demonstrated to play an important role in the acquisition and expression of fear responses based on the animal model of fear conditioning (Davis 1992; LeDoux 1993) and therefore has been hypothesized to play a role in symptoms of PTSD. Although some studies found activa-

tion of the amygdala during stimulation of PTSD symptoms in PTSD patients (Rauch et al 1996; Shin et al 1997), others have not (Bremner et al 1997a, 1999a, 1999b; Shin et al 1999). Also, some studies have found decreased function in left inferior frontal gyrus (Rauch et al 1996; Shin et al 1997, 1999), whereas others have not (Bremner et al 1999a, 1999b). It is likely that the specific task employed has an effect on recruitment of specific regions of the stress circuit. For instance, excessive amygdala function may be seen primarily in conditioned fear responses and response to exteroceptive threats, which are not specifically a part of the cognitive/behavioral response invoked by the current paradigm.

There are several cautions that should be mentioned regarding the current study. This study did not involve a control group with a history of abuse without PTSD. Therefore, we cannot conclude that the current findings are associated specifically with PTSD, as opposed to being

a nonspecific aspect of abuse. The word lists were presented in a fixed order and were not counterbalanced, raising the possibility of order effects in the results. Although the between-group comparisons should control for possible order effects, there is the possibility that different groups may respond to the order differently (e.g., PTSD patients may become more anxious toward the end of the scan session and have correspondingly different patterns of brain activation). Because we studied a homogeneous group of women with abuse-related PTSD, we cannot generalize the results to other PTSD populations or to men with PTSD. Also, we did not match patients and control subjects for racial or ethnic status; however, we are not aware of any studies showing racial differences in memory or emotional processing. The PTSD women in this study had high rates of comorbid conditions, which is typical of PTSD. We have elected not to exclude PTSD patients with comorbid affective and anxiety disorders, or past histories of alcohol/substance abuse, as this will result in an unrepresentative and possibly biased study population. There is, however, a possibility that the results are related to comorbid conditions rather than PTSD. Finally, this is a cross-sectional study, and we cannot infer from the results that PTSD and/or abuse cause changes in the circuitry outlined in the results. There are a number of other factors that could explain the results, ranging from genetics to environmental factors that are associated with the PTSD condition.

Future studies are required to extend our knowledge of the neural circuitry of PTSD. The current study should be repeated to compare PTSD women with non-PTSD women with a history of abuse. Also, it is important to determine whether these findings will differ in PTSD populations with different trauma histories and in men with PTSD. Future studies in PTSD should go beyond the use of symptom provocation, and expand our knowledge of the neural circuitry of PTSD by using paradigms, such as that used in the current study, that invoke the circuitry with emotionally valenced declarative memory. Future studies are also needed to assess the effect of treatments on the neural circuitry of PTSD.

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